

REMARKS

New claims 30-49 appear in this application for the Examiner's review and consideration. These claims are re-written versions of the prior claims, namely claims 1-4, 29, 6-8, 25-28, and 17-24, respectively. Claims 35 and 47, previously appearing as claims 6 and 22, have been amended as noted below, but these amendments are fully supported by the specification so that there is no issue of new matter. Thus, these new claims should be entered into the application at this time.

Claims 6-7 and 21-28 were rejected under 35 U.S.C. 112, first paragraph. The office action states that the specification, while being enabling for compositions useful in treating and managing the claimed maladies, does not enable preventing those maladies.

In response, Applicants have prepared new claims 35 and 47 to recite "preventing the symptoms of" instead of "preventing" the disease. The specification is fully enabling with regard to preventing the symptoms of diseases. For example, in the arachidonic acid (AA) induced ear inflammation model in the mouse, HU-308 was injected between 30 to 90 minutes before application of AA (specification, line 18, page 9; Fig. 6). In the peripheral pain model HU-308 was injected 90 minutes before formalin induction (specification, line 31, page 22; Fig. 7). In both cases, the results support preventive effect of HU-308 (Figs. 6 and 7). Thus, the present invention is enabling regarding the prevention of the symptoms of diseases. For this reason, the section 112 rejection is inapplicable against the new claims.

Claim 4 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Specifically, the office action objects to the recitation of a variable labeled "Q." Applicants have drafted new claim 33 which now replaces claim 4 to cover preferred compounds without referring to constituent Q. Thus, the prior rejection is inapplicable to new claim 33.

Claims 1-3, 6-7 and 17-29 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,434,295 to Mechoulam et al. (hereafter "Mechoulam") (Applicants note that the Examiner cites Mechoulam as "09/698,071" but Applicants believe that the Examiner intends that to mean Patent No. 5,434,295 according to the PTO 892 list of references attached to the Office Action). Applicants respectfully traverse the rejection.

Mechoulam discloses certain novel 4-phenylpinene derivatives. Mechoulam also utilizes those derivatives in pharmaceutical compositions that are useful in treating problems relating to the central nervous system ("CNS") (col. 1, lines 9-14).

First of all, Mechoulam does not disclose the specific compounds that are defined by the present claims. In particular, Mechoulam does not disclose the claimed combination of

R₁ and G groups. Furthermore, these compounds provide unexpected results compared to the compounds that are disclosed in the Mechoulam patent.

The compounds synthesized by Mechoulam are non-psychotropic and, as such, are presumed not to bind to cannabinoid receptors at all. In fact, binding to CB₁ receptors, which are the major receptors of the CNS, is what induces undesired psychotropic effects and this must be avoided in the design and selection of these compounds for therapeutic uses. Mechoulam does not mention or test any of the compounds disclosed in his patent for their ability to bind a peripheral receptor, i.e., one that is not a major CNS receptor.

In contrast, Applicants in the present invention have unexpectedly discovered that the present compounds bind to CB₂ receptors, i.e., to bind to the peripheral non CNS receptors which appear mainly on lymphocytes. As disclosed in the present invention, HU-308 binds CB₂ with a $K_i = 22.7 \pm 3.9$ nM and a specificity of above 400 fold relative to CB₁ (page 10 lines 22-23). Such a high binding affinity and selectivity confer a clear therapeutic potential to HU-308. This therapeutic potential is not disclosed or even mentioned anywhere in Mechoulam, most likely because the compounds disclosed in his patent do not possess these binding affinity and selectivity properties.

Applicants further unexpectedly found that binding to CB₂ receptors confers on these compounds utilities in the treatment of CB₂ mediated disorders including hypertension, pain, GI disorders, and autoimmune diseases, as well as tumors expressing CB₂ receptors. These unexpected utilities were neither disclosed in nor suggest by the Mechoulam patent or any other prior art references. It is submitted that these unexpected benefits support the patentability of the present claims.

The office action requested that a side-by-side comparison of HU-308 with the closest prior art compound, i.e., Mechoulam's HU-255 compound, to demonstrate the unexpected features of the present invention. In this regard, applicants note that in Mechoulam no activity is disclosed or tested for HU-255 since this compound is merely presented as an intermediate in the synthesis of HU-259. If the HU-255 compound was believed to be a preferred one, or if it possessed highly advantageous benefits, Mechoulam certainly would have mentioned this. When HU-255 was eventually tested for binding to cannabinoid receptors, it was found to have an IC₅₀ of 36 nM for CB₁ and an IC₅₀ of 5.6 nM for CB₂ in specific radioligand displacement assays. In other words, HU-255, the closest prior art compound, possess has no significant CB₂/CB₁ selectivity with a ratio of only about 6. This is seventy fold lower than that of the present HU-308 compound. Clearly, the superior results

for HU-308 are far from obvious or expected based on the disclosure of HU-255 in the Mechoulam patent. Claims 40-41 and 45-46 are directed to this compound.

The remaining compounds recited in the present claims are closely related lower alkyl or hydrogenated derivatives of HU-308. As such, the unexpected results for HU-308 also support the patentability of such compounds. Accordingly, the obviousness rejection is not applicable to any of the compounds that are recited in the present claims.

Furthermore, claim 40 is further distinguishable from the Mechoulam patent because it is directed to a CB2 specific agonist. As Mechoulam's compounds do not possess this feature, there is no teaching or motivation for the skilled artisan to even look to those compounds or any modifications thereof in an attempt to develop such agonists.

In view of the above, the entire application is believed to be in condition for allowance, early notice of which would be appreciated. Should any issues remain, a personal or telephonic interview is respectfully requested to discuss the same in order to expedite the allowance of all the claims in this application.

No fee is believed to be due for this submission. Should any fees be due, however, please charge such fees to Winston & Strawn Deposit Account No. 501-814.

Respectfully submitted,

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